

## NOVEL THIENOPYRIDINES AS POTENT PLATELET INHIBITORS: FUTURE TREATMENTS FOR PLATELET HYPERACTIVITY DISORDERS?

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**Background:** Platelet hyperactivity is associated with a number of disorders including Acute Coronary Syndromes (ACS) and manifests as increased platelet activation and often inappropriate thrombus formation. The thienopyridine class of anti-platelet drugs, of which clopidogrel and prasugrel are the most well-known, target the P2Y<sub>12</sub> receptor on platelets, blocking the effects of the platelet agonist ADP. However, the effect of these drugs is variable amongst patients, with some patients responding well and some remaining at risk of thrombosis. This variability highlights a need for a refinement of this class of P2Y<sub>12</sub> inhibitor.

**Aims:** The aim of this study was to assess the efficacy of six novel thienopyridine derivatives synthesized by our group by examining their potential as *in-vitro* inhibitors of platelet function.

**Methods:** Healthy human platelets were isolated and incubated with novel thienopyridine compounds (DJ0081, DJ0199, DJ0021, DJ0206, DJ0171, DJ0097) (10µM, 30min) prior to stimulation with ADP (10µM) and analysis of alpha granule secretion (CD62P expression), GPIIb/IIIa activation (PAC1 expression) and platelet leukocyte aggregate (PLA) formation using flow cytometry.

Furthermore, light transmission aggregometry (LTA) was used to assess ADP-stimulated aggregation after these treatments. As clopidogrel is usually prescribed in combination with the COX-1 inhibitor acetylsalicylic acid (ASA), synergy of the novel compounds with ASA (30µM) was also analysed by LTA. All results were compared to ADP-stimulated samples and samples treated with clopidogrel (10µM, 30min) prior to ADP stimulation.

**Results:** All six novel compounds demonstrated a significant reduction in ADP-mediated platelet aggregation ( $P < 0.001$ ), CD62P expression ( $p < 0.001$ ), PAC1 expression ( $p < 0.01$ ) and PLA formation ( $p < 0.05$ ). These compounds were also shown to enhance the inhibitory effects of ASA. DJ0171 and DJ0199 were particularly potent, displaying greater inhibitory effect than clopidogrel.

**Summary/Conclusion:** The study demonstrates the potential for new thienopyridine compounds as modulators of platelet function and points to the possibility of future use in patients at risk of platelet hyperactivity and thrombosis.

**Keywords:** Inhibitor, Platelet activation, Platelet aggregation, Thrombosis